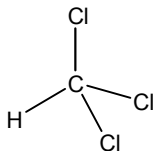


CHLOROFORM

CAS No. 67-66-3

First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

Chloroform(CHCl₃) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (NCI, 1976b; IARC V.1, 1972; IARC V.20, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered by gavage (in corn oil), the compound induced hepatocellular carcinomas in mice of both sexes. It also induced increased incidences of kidney epithelial tumors in male rats when administered by the same route (NCI, 1976b). When administered orally (in olive oil), chloroform induced hepatomas and cirrhosis in female mice (IARC V.20, 1979). Chloroform in toothpaste or arachis oil, administered to four strains of mice by gavage, induced kidney epithelial tumors in males of one strain (Roe et al., 1979). When administered orally in drinking water, chloroform induced increased incidences of renal tubular cell adenomas and/or adenocarcinomas in male rats, but no renal or hepatic tumors were induced in male or female mice (Jorgenson et al., 1975). Another recent study reported the development of hepatic adenofibrosis in rats of both sexes and neoplastic nodules in females when chloroform was administered in the drinking water (Tumasonis et al., 1987).

There is inadequate evidence for the carcinogenicity of chloroform in humans (IARC S.4, 1982; IARC S.7, 1987). Several epidemiological and ecological studies indicate that there is an association between cancer of the large intestine, rectum, and/or urinary bladder and the constituents of chlorinated water (OHEA, 1985a). Although data may suggest a possible increased risk of cancer from exposure to chloroform in chlorinated drinking water, the data are insufficient to evaluate the carcinogenic potential of chloroform.

PROPERTIES

Chloroform is a colorless, volatile liquid that is nonflammable. It is slightly soluble in water and is miscible with oils, ethanol, ether, and other organic solvents. Chloroform has a pleasant, nonirritating odor. It is unstable when exposed to air, light, and/or heat, which cause it to break down to phosgene, hydrochloric acid, and chlorine. It is usually stabilized by the addition of 0.6%-1% ethanol. When heated to decomposition, chloroform emits toxic fumes of hydrochloric acid and other chlorinated compounds.

USE

Chloroform is used primarily in the production of fluorocarbon-22 (93% of the chloroform produced). Fluorocarbon-22 is used as a refrigerant (70% of the fluorocarbon-22 produced) and in the production of fluoropolymers (30%). Miscellaneous uses of chloroform (4%) include use as a solvent in the extraction and purification of some antibiotics, alkaloids, vitamins, and flavors; as a solvent for lacquers, floor polishes, artificial silk manufacture, resins, fats, greases, gums, waxes, adhesives, oils, and rubber; as an industrial solvent in photography and dry cleaning; as a heat

transfer medium in fire extinguishers; and as an intermediate in the preparation of dyes and pesticides (Chem. Mktg. Rep., 1976c). It is also used in certain medical procedures, such as dental root canal surgeries, and in combination with other ingredients as an experimental treatment of herpes zoster or for control of screw worm in animals, but its use as an anesthetic has been largely discontinued (Kirk-Othmer V.5, 1979; ATSDR, 1997-R024). At least one grain fumigant mixture had contained chloroform with carbon disulfide (Kirk-Othmer V.5, 1979).

PRODUCTION

One U.S. manufacturer began chloroform production in 1903, but commercial production was not reported until 1922 (IARC V.20, 1979). Since the early 1980s, the production of chloroform has increased by 20-25%, primarily due to the great demand for the refrigerant HCFC-22 (ATSDR, 1997-R024). In 1994, 565 million Lb of chloroform was produced in the US (Chem. Eng. News 1987a and 1996).

Imports of chloroform have shown a decrease from a high of 38 million lb in 1989 to 5.3 million lb in 1994. Exports have increased overall from the mid-1980s through the mid-1990s with 93 million lb being exported in 1994 (ATSDR 1997-R024; Chem. Week 1986b; USDOC Consum. 1984; USDOC Exports 1986 and 1990; and USDOC Imports 1990).

EXPOSURE

The primary routes of potential human exposure to chloroform are ingestion, inhalation, and dermal contact with water (e.g., while showering, swimming, cleaning, and cooking). Therefore, all humans are exposed to low levels of the chemical (NCI, 1976b; IARC V.20, 1979; ATSDR, 1997-R024). Ingestion of contaminated water is expected to be a major source since most drinking water supplies may contain chloroform as a by-product of chlorination for disinfection purposes. The concentration of chloroform in drinking water increases with time; typical levels range from 2 to 68 ppb. Foods such as dairy products, oils/fats, vegetables, bread, and beverages may also contain small amounts of chloroform; typical average levels range from 52 to 71 $\mu\text{g}/\text{kg}$. Chloroform has been detected in the atmosphere at concentrations ranging from 0.02 to 13 $\mu\text{g}/\text{m}^3$ and in indoor air at 0.07 to 3.6 $\mu\text{g}/\text{m}^3$ (ATSDR, 1997-R024). Exposure via inhalation results in 60 to 80% absorption. Placental transfer of chloroform has also been demonstrated (IPCS, 1994b).

Bathing or showering with chlorinated tap water can expose a person to chloroform via all three routes. A recent investigation has shown that water temperature exerts a very strong effect on dermal absorption of chloroform while bathing (Gordon et al., 1998). Among ten subjects, the mean amounts of chloroform exhaled at the lowest bath-water temperature (30 °C) was 0.2 μg , while at the highest temperature (40 °C) it was 7 μg , a factor of almost 30. This is explained by the heat-conserving or heat-dissipating mechanisms of the body, where at low bath-water temperatures the capillaries closest to the skin's surface experience decreased blood flow, which forces the chloroform to diffuse across a greater distance to reach the blood. At high bath-water temperatures, the opposite occurs.

While great attention has been on trihalomethane exposures resulting from routine ingestion of chlorinated water, Lindstrom et al. (1997) recently undertook the effort of examining dermal and inhalation exposures that occur in a residential setting. In this case, the common recreational sport of swimming was studied observing two college students (one male and one female) during a typical two-hour workout. Chloroform breath concentrations, found to be as high as 371 $\mu\text{g}/\text{m}^3$ and 339 $\mu\text{g}/\text{m}^3$ for the subjects, respectively, were more than two times the maximum possible

inhalation-only level. Furthermore, the maximum alveolar breath concentrations ultimately rose to more than twice the indoor chloroform level, suggesting that the dermal pathway is the major means of exposure to chloroform versus the inhalation route; the dermal contribution was estimated at greater than 80%.

Occupational exposure may occur during the manufacture of chloroform or during one of its uses. Persons working at waste water and other treatment plants can be exposed to significant levels of the chemical (ATSDR, 1997-R024). Other industries using chloroform include building and paperboard industries, iron and steel manufacturing, internal combustion engine industries, pesticide manufacturing, breweries, dry cleaning, and food processing industries. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 215,000 workers were potentially exposed to chloroform in the workplace (NIOSH, 1976). The National Occupational Exposure Survey (1981-1983) indicated that 95,330 total workers, including 40,973 women, potentially were exposed to chloroform (NIOSH, 1984). The Toxic Chemical Release Inventory (EPA) listed 167 industrial facilities that produced, processed, or otherwise used chloroform in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of chloroform to the environment which were estimated to total 23.9 million lb. In the more recent 1993 inventory, chloroform was a chemical intermediary, impurity, or waste by-product at 172 facilities (ATSDR, 1997-R024). The ACGIH recommends a threshold limit value of 10 ppm as an 8-hr time-weighted average (TWA) (ACGIH, 1996).

REGULATIONS

EPA regulates chloroform under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Chloroform is a toxic pollutant of air and water. EPA has established water quality criteria for chloroform, effluent guidelines, rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of chloroform wastes. A reportable quantity (RQ) of 10 lb has been established for chloroform under CERCLA and CWA. Chloroform is exempted under FD&CA from tolerances for pesticide chemicals. Chloroform is recognized as an inert ingredient of toxicologic concern under FD&CA. A rebuttable presumption against registration of chloroform-containing pesticides has been issued under FIFRA. Chloroform is regulated as a hazardous constituent of waste under RCRA. EPA requires removal of chloroform from drinking water and establishes a maximum contaminant level (MCL) of 100 µg/L under SDWA. Under EPCRA, EPA identifies chloroform as an extremely hazardous substance and established a threshold planning quantity (TPQ) of 10,000 lb for chloroform. FDA regulates chloroform as an indirect food additive for adhesive components in food packaging materials and as a component of materials that come into contact with food. The use of chloroform in food, drugs (for both humans and animals), and cosmetics for use in cough preparations, liniments, cosmetics, and toothache drops is banned under FD&CA. NIOSH recommends a 2-ppm short-term exposure limit (STEL; 60 minutes) (NIOSHc, 1994). OSHA has established a permissible exposure limit (PEL) of 2 ppm with no provision for a ceiling. OSHA regulates chloroform under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-22.